



## Review Article

## Early detection of early gastric cancer using image-enhanced endoscopy: Current trends



Mingjun Song, Tiing Leong Ang\*

## A B S T R A C T

Image-enhanced endoscopy refers to techniques of enhancing mucosa surface contrast with the ultimate aim of improving lesion detection and diagnosis. It is vital to detect early gastric cancer as it may be possible to perform curative endoscopic resection. In this topic review, we summarize the options available, such as the traditional dye-based chromoendoscopy, as well as the newer equipment-based techniques such as narrow-band imaging, flexible spectral imaging color enhancement, and i-scan. We further discuss in greater detail the technique of narrow-band imaging combined with magnifying endoscopy, and how this has facilitated lesion characterization and diagnosis based on characteristic abnormal microvascular and microsurface features. Other endoscopic imaging modalities such as autofluorescence imaging and endoscopic microscopy are also briefly discussed.

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Keywords: Early gastric cancer, Gastroscopy, Narrow band imaging, Magnifying endoscopy

## Introduction

Globally, gastric cancer is the fourth most common cancer in men, the fifth most common cancer in women, and the second leading cause of death due to cancer. About 10% of annual cancer deaths worldwide are attributed to gastric cancer, which means that gastric cancer has a high fatality to case ratio of about 70%.<sup>1</sup> The highest incidence rates for gastric cancer occur in East Asia (China, Mongolia, Korea, and Japan).<sup>2,3</sup> Gastric cancer is histologically divided into two types in the Lauren classification: intestinal (with intercellular junctions) and diffuse (without intercellular junctions).<sup>4</sup> More than 90% of gastric cancers are intestinal-type adenocarcinoma, which is believed to be preceded by a “precancerous cascade,” progressing in a sequential manner from chronic gastritis, atrophic gastritis, intestinal metaplasia, and adenoma to early gastric cancer (EGC).<sup>5</sup>

The overall prognosis of gastric cancer is dismal; the average 5-year survival rate is less than 20% and EGC are often clinically silent. However, if the cancer is detected and endoscopically resected prior to invasion into the muscularis propria occurs, the 5-year survival rate can reach 90%.<sup>6</sup> EGC, a term defined by Japanese researchers in 1962, is meant to denote the curable phase of the disease when cancer cells are confined within the mucosal or submucosal layer (T1 cancer) regardless of the presence of lymph node metastasis.<sup>7</sup> Endoscopic resection using the endoscopic mucosal resection (EMR) technique or endoscopic submucosal dissection (ESD) is potentially curative for the patient if there is no nodal metastasis, and can avoid the morbidity associated with

gastrectomy. Candidates for EMR are patients with EGC that is differentiated adenocarcinoma, is less than 2 cm, has no ulceration, and has no lymphovascular involvement.<sup>8</sup> Gotoda et al<sup>9</sup> reviewed surgical pathological data and found that differentiated cancers less than 3 cm in diameter and undifferentiated cancers less than 2 cm in diameter had negligible nodal metastasis. Submucosal cancers that were differentiated, were less than 3 cm in diameter, and invaded less than 500  $\mu$ m into the submucosal were also free of nodal metastasis.<sup>9</sup> Another large study involving 5265 patients found similar results and proposed that endoscopic resection should be considered for undifferentiated intramucosal cancers, which are less than 2 cm in diameter and has no ulcerative findings or lymphovascular involvement, as the risk of lymph node metastasis was negligible.<sup>10</sup> This led to expanded criteria for endoscopic resection. *En bloc* resection is crucial for accurate histopathological assessment and, in the context of lesions larger than 2 cm or in the presence of fibrosis or ulceration, ESD rather than EMR would be the technique of choice.

Thus, the early detection of EGC is important. However, the sensitivity of conventional white light imaging (C-WLI) in detecting EGC had been reported to range only from 77% to 84%.<sup>11</sup> Image-enhanced endoscopy (IEE) involves the use of dyes, optical methods (by manipulation of the light source), and electronic methods (by manipulation of captured light), to increase the contrast of surface structure, and thus improve visualization and diagnostic accuracy. There are three different commercially available systems for equipment-based IEE: (1) narrow-band imaging (NBI; Olympus Corporation, Tokyo, Japan); (2) flexible spectral

Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore

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\* Corresponding author. Department of Gastroenterology, Changi General Hospital, 2 Simei Street 3, 529889, Singapore.

E-mail address: [tiing\\_leong\\_ang@cgh.com.sg](mailto:tiing_leong_ang@cgh.com.sg) (T.L. Ang).

imaging color enhancement (FICE; Fujifilm, Tokyo, Japan); and (3) i-scan (Pentax, Tokyo, Japan). IEE can be combined with magnifying endoscopy to further characterize focal lesions. This review will focus on the utility of IEE techniques and briefly discuss other endoscopic imaging modalities such as autofluorescence imaging (AFI) and endoscopic microscopy.

### Chromoendoscopy

Chromoendoscopy involves the spraying of a dye onto the gastric mucosa after a complete inspection with C-WLI to highlight any subtle mucosal irregularities that could have been missed. Absorptive dye such as methylene blue is actively absorbed by intestinal epithelium, therefore highlighting the area of intestinal metaplasia. Contrast dyes such as indigo carmine have no cellular staining; the dye pools in the crevices of the lesion and accentuates its border and surface topography (Fig. 1A and B). This significantly helps detect nonpolypoid EGC. In some centers in Japan, diluted indigo carmine is routinely sprayed throughout the stomach after a complete screening examination.<sup>12</sup>

### NBI

NBI is an endoscopic technique that uses narrow bandwidth filters in the red–green–blue sequential illumination system. The filters are enabled or disabled during endoscopy by pushing a button to limit the wavelengths of light to that of blue (400–430 nm) and green (430–460 nm) via the mechanical insertion of a narrow band filter in front of the xenon arc lamp. Blue and green light penetrate less deeply into the gastric mucosa and are preferentially absorbed by hemoglobin so that vessels appear dark colored. On the endoscopy monitor, the signals obtained from the blue and green filters are combined to form an image that highlights the vasculature on the superficial mucosa.<sup>13–15</sup> However, owing to the weak light intensity and the large size of the gastric lumen, the images obtained by NBI alone tend to be very dark, which significantly limits its utility for endoscopic screening and surveillance of gastric lesions.<sup>16</sup> Newer generation NBI processors (290 and 190 series) with higher light intensities have been developed and may potentially improve detection rates.<sup>17</sup>

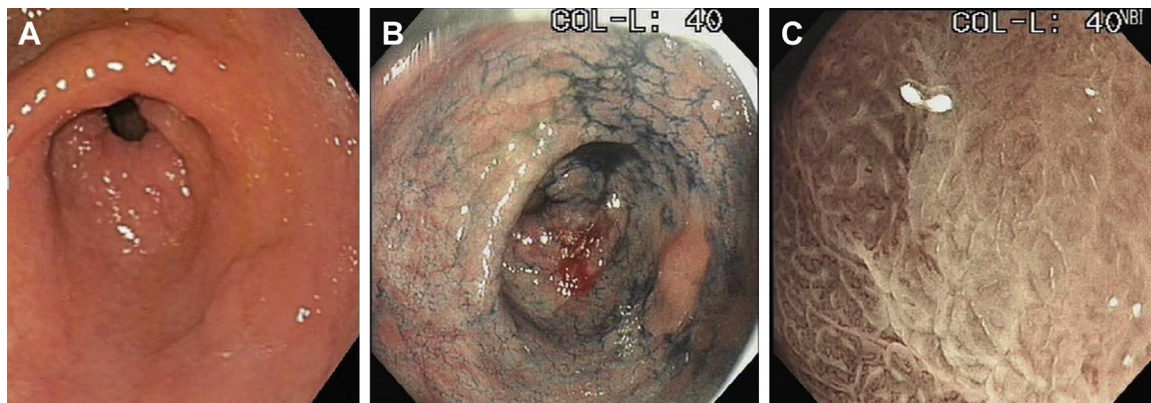
### FICE and i-scan

FICE is a spectral estimation technique that enhances the contrast of mucosal surfaces. The white-light image captured by the endoscope is sent to a spectral estimation matrix processing circuit.

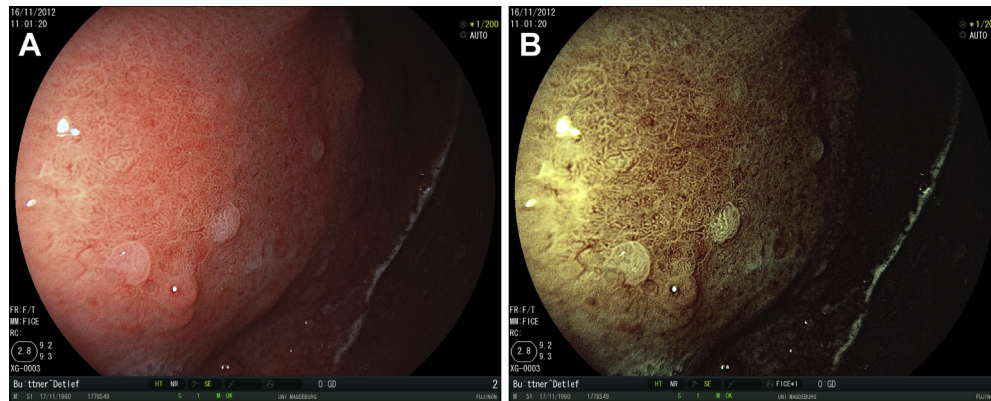
FICE processes the image into spectral images composed from a single wavelength and then displays them in real time. Unlike NBI, FICE is software driven and does not use optical filters. The wavelengths used with FICE are associated with laminar structures and blood flow in the gastrointestinal mucosa altered by inflammation or neoplasm, which acts as a scattering element and interferes with the reflectance spectrum. Like NBI, the operator can switch between the white-light image and the FICE image by a simple push of a button on the endoscope, and this technology can be coupled with optical or digital magnification.<sup>18</sup> The better contrast between the malignant lesion and the surrounding normal mucosa significantly helps in accurately diagnosing the lateral extent of gastric cancer compared to C-WLI (Fig. 1C, Fig. 2A and B).<sup>19</sup> i-Scan is another digital contrast method applying postprocessing algorithms to white light images to enhance the image contrast.<sup>17</sup> There are three modes: surface enhancement mode, contrast enhancement mode, and tone enhancement mode. Similar to FICE, i-scan uses software to improve the contrast of gastric lesions against the normal mucosa (Fig. 3A and B). In contrast to NBI, for which there are abundant data concerning its utility in the diagnosis of EGC, the published data concerning the performance characteristics of FICE and i-scan in the diagnosis of EGC are limited.

### Magnifying endoscopy

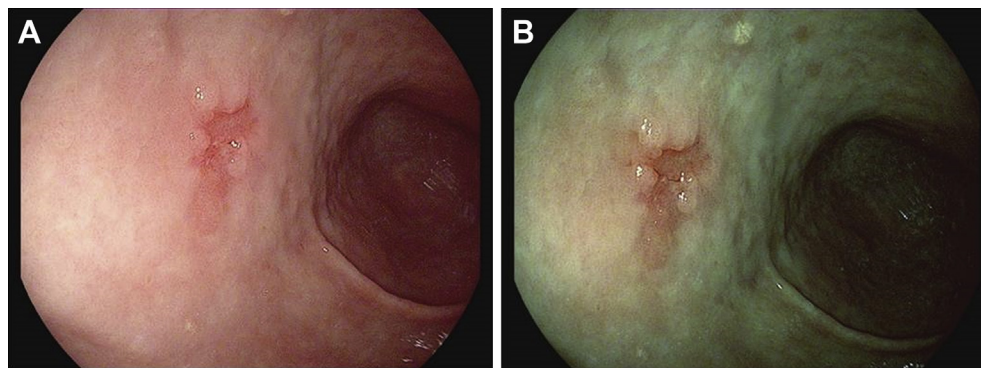
Standard high definition (HD) endoscopy can enlarge an image up to 30 times, whereas high-magnification endoscopy (ME) can enlarge an image up to 100 times. In terms of image resolution, optical zoom, in which a zoom lens is connected to the endoscope tip, is superior to digital zoom or electronic magnification.<sup>20</sup> Digital zoom relies on signal processing to enlarge images obtained from the charged-couple device (CCD), and this tends to decrease image quality. To optimize ME, adequate preparations are required. There must be optimal cleansing of the mucosal surface, such as with diluted 0.04% simethicone solution and mucolytics, to remove mucus and foam. HD white light endoscopy should be used. A soft black hood is essential; this should be mounted on the endoscopy tip to allow the endoscopist to consistently fix the mucosa at about 2–3 mm from the lens to allow maximal magnification and optimal image resolution. The entire mucosal surface should be carefully surveyed without magnification first; when a suspicious lesion is detected, the lesion should be inspected selectively by magnification in order to visualize the fine patterns and capillaries on the mucosa. ME, when combined with IEE, can clarify the microvascular and microsurface features and facilitate lesion characterization and diagnosis.



**Fig. 1.** Image enhanced endoscopy appearance of gastric adenoma. (A) White light endoscopy image of gastric adenoma with 0-IIa morphology. (B) Margins of gastric adenoma are accentuated by indigo carmine chromoendoscopy. (C) Narrow band magnifying image of gastric adenoma with regular microvascular and microsurface patterns.



**Fig. 2.** Image enhanced endoscopy appearance of early gastric cancer. (A) White light endoscopy image of early gastric cancer. (B) Enhancement of the mucosal surface structure of early gastric cancer by flexible spectral imaging color enhancement (FICE) (A and B are courtesy of Fujifilm, Tokyo, Japan.).



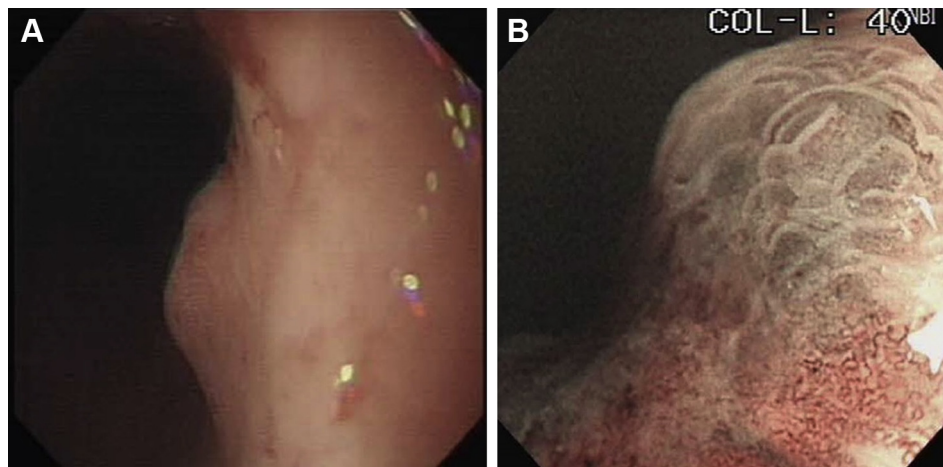
**Fig. 3.** Image enhanced endoscopy appearance of early gastric cancer. (A) White light endoscopy image of early gastric cancer. (B) Enhancement of the mucosal surface structure of early gastric cancer by i-scan (A and B are courtesy of Dr. Joo Young Cho and Dr Won Young Cho, Soon Chun Hyang University Hospital Seoul Korea.).

#### NBI combined with ME

The potential of NBI for diagnosis of EGC is maximized when combined with ME.<sup>21</sup> The microvascular architecture and the microsurface structure can then be clearly visualized to facilitate detection of changes of metaplasia, dysplasia, or cancer and to detect an important line of demarcation from the surrounding normal mucosa (Figs. 1C, 4A, and 4B).<sup>22</sup> The Paris classification for superficial gastrointestinal neoplasia divides the lesion into three

main categories: superficial elevated (0-IIa) type, superficial flat (0-IIb) type, and superficial depressed (0-IIc) type.<sup>23</sup> For the 0-IIb and 0-IIc types of gastric neoplasia, NBI combined with ME (NBI-ME) has been shown to be useful for distinguishing between benign and malignant lesions based on the abnormal microvascular pattern in malignant lesions.<sup>24,25</sup>

Using NBI-ME, endoscopists have been able to discern carcinomatous gastric lesions from benign gastric lesions. Many classification systems have been introduced to describe these NBI-ME



**Fig. 4.** Image enhanced endoscopy appearance of early gastric cancer. (A) White light endoscopy image of early gastric cancer. (B) Narrow band magnifying image of early gastric cancer showed irregular microvascular and microsurface patterns.



findings. The most commonly adopted classification is the VS classification introduced by Yao and colleagues.<sup>26</sup> “V” stands for the vascular pattern of microvessels. The regular pattern consisted of mucosal capillaries with uniform thickness and a symmetrical arrangement of closed-loop (polygonal) or open-loop shapes. The irregular pattern consisted of vessels that differed in shape and size and was asymmetrically distributed over the lesion. “S” stands for surface microstructure such as crypt epithelium and the presence of white opaque substance (WOS). In a regular surface pattern, the crypt epithelium has a constant width and a uniform structure, which may be round, oval, tubular, curved, or papillary. When WOS is present, it tends to be arranged in a well-organized and symmetrical reticular, maze-like, or speckled pattern. In irregular surface patterns, the crypt epithelium has variable width and the distribution and arrangements are irregular and asymmetrical. The WOS, if present, tends to also be in an irregular reticular or speckled pattern of asymmetrical distribution.<sup>26</sup> WOS is attributable to lipid deposition within the neoplastic epithelium.<sup>27,28</sup>

The characteristic NBI-ME findings of EGC include an irregular microvascular pattern with a demarcation line and/or an irregular microsurface pattern with a demarcation line. In a study by Yao et al,<sup>26</sup> 97% (97/100) of EGC fulfilled either one or both of these criteria. The three cases that did not meet the VS classification criteria were poorly differentiated carcinomas that were found on histological examination to have invaded sparsely and diffusely into the lamina propria beneath the surface epithelium. This was the reason why these three lesions did not have obvious disturbance in the microvascular or microsurface pattern and had no distinct demarcation line from the surrounding mucosa. Yao et al<sup>29</sup> also reported that WOS was more frequently seen in gastric adenomas compared to gastric carcinomas (78% vs. 43%,  $P < 0.05$ ), and the pattern of WOS was of a regular pattern in all adenomas, but of an irregular pattern in 83% of the carcinomas ( $P < 0.0001$ ). This showed that although WOS obscured the visualization of microvascular pattern, it could also be useful as an optical sign to help investigators determine if a lesion is malignant.

Kaise et al<sup>30</sup> suggested another way of detecting cancerous lesions with NBI-ME by focusing on specific features that are more unique to malignancy: the disappearance of fine mucosal structure, the dilatation of microvasculature, and the heterogeneity of the surface pattern. In the evaluation of 0-IIb or 0-IIc lesions based on this diagnostic triad, NBI-ME achieved a diagnostic sensitivity of 92.9% and a specificity of 94.7% compared with WLI, which only had a diagnostic sensitivity of 42.9% and a specificity of 61.0%.<sup>30</sup>

Nakayoshi et al<sup>31</sup> conducted a prospective study to measure the correlation between diagnosis made based on magnifying NBI findings and the actual histology result of 0-IIc EGC lesions. They broadly classified the microvascular network into three general patterns: A, fine network pattern (FNP); B, corkscrew pattern (CSP); and C, unclassified pattern.<sup>31</sup> They compared the microvascular pattern trends between undifferentiated adenocarcinoma lesions and differentiated adenocarcinoma lesions to see if NBI-ME was capable of predicting the histological characteristics of gastric cancer lesions. They found that differentiated adenocarcinomas tend to have FNP (66.1% vs. 3.7%), whereas undifferentiated adenocarcinomas tend to have CSP (85.7% vs. 3.6%,  $P = 0.0011$ ). However, 30.3% of the differentiated adenocarcinomas and 10.7% of the undifferentiated adenocarcinomas had “unclassified” microvascular pattern on NBI-ME.

Yokoyama et al<sup>32</sup> introduced two additional categories to describe the abnormal microvascular pattern and irregularity of superficial glandular structure of EGC: intralobular loop pattern 1 (ILL-1) and intralobular loop pattern 2 (ILL-2). In ILL-1, there is a villous glandular structure with loop-like microvessels in it. In ILL-2, the villous glandular structure shows the areas of destruction and the microvessels

do not show a complete “loop”. These four categories follow a gradient of increasing distortion to the mucosal surface—from FNP, to ILL-1, to ILL-2, and finally to the highly irregular CSP. Yokoyama et al<sup>32</sup> did not limit this study to only 0-IIc EGC lesions; 0-IIa and 0-IIb lesions were also included. In determining the pattern category, the predominant visible pattern was used. They were able to classify all 223 differentiated adenocarcinomas and 54 undifferentiated adenocarcinomas. There were no “unclassified” lesions, but they had stated that cases with an ulcer with white fibrin were excluded from the study analysis. Their results showed that differentiated adenocarcinomas mainly showed ILL-1 (133/223 lesions) and very little showed CSP (1/223 lesions). By contrast, undifferentiated lesions had predominantly CSP (20/34 lesions) and ILL-2 lesions (14/54 lesions). Overall, 41.2% of the undifferentiated cancers had ILL-2, whereas 24.2% of the differentiated cancers had ILL-2.

NBI-ME has been proven to be superior to C-WLI, ME, and chromoendoscopy in gastric cancer detection and the determination of tumor margins. With C-WLI, red discoloration, mucosal ulceration, and depressed lesions are associated with higher likelihood of carcinoma.<sup>33</sup> Maki et al<sup>34</sup> compared C-WLI with NBI-ME and found that NBI-ME had significantly higher sensitivity (95% vs. 64%) and accuracy (92% vs. 74%) in detecting EGC. However, in elevated lesions with red discoloration, the specificity of NBI-ME and C-WLI was comparable (88% vs. 94%). Tsuji et al<sup>35</sup> showed that NBI-ME was significantly better than C-WLI in distinguishing adenomas from carcinomas. In their retrospective study, 37 cases were selected that were diagnosed as gastric adenomas based on C-WLI findings and pretreatment forceps biopsy. The presence of irregular microvascular or microsurface pattern with demarcation line on NBI-ME was significantly correlated with the final pathological diagnosis of carcinoma (odds ratio 13.68, 95% confidence interval 5.69–32.88,  $P < 0.001$ ). Kato et al<sup>36</sup> compared the yield of C-WLI and NBI-ME in patients who underwent endoscopic surveillance for synchronous or metachronous gastric cancer. The sensitivity and specificity for ME-NBI for diagnosis of gastric cancer (92.9% and 94.7%, respectively) were significantly better than those for CWLI (42.9% and 61.0%, respectively). A single-center study first showed that NBI-ME had a better diagnostic accuracy in differential diagnosis of gastric small depressive lesions compared to ME; the diagnostic accuracy for gastric cancer in NBI-ME was 79% (45/57 lesions) versus 44% (25/57 lesions) in ME.<sup>37</sup> This was later substantiated by a multicenter, prospective, randomized, controlled trial that compared C-WLI to NBI-ME in patients with undiagnosed depressed gastric lesions less than 10 mm in diameter. The diagnostic accuracy of NBI-ME was significantly better than that of C-WLI (90.4% vs. 64.8%,  $P < 0.001$ ), whereas the diagnostic sensitivity of NBI-ME was higher but not as statistically significant (60.0% vs. 40.0%,  $P = 0.34$ ). However, combining C-WLI with NBI-ME significantly increased both diagnostic accuracy (from 64.8% to 96.6%,  $P = 0.001$ ) and diagnostic sensitivity (from 40.0% to 95.0%,  $P = 0.001$ ).<sup>38</sup> The usefulness and limitations of NBI-ME when chromoendoscopy was unsuccessful for determining the horizontal extent of EGC was examined in a case series of 350 consecutive EGC resected *en bloc* by ESD. The proportion of cancers showing unclear margins by chromoendoscopy was 18.9% (66/350). Of these, 62/66 were examined by NBI-ME, and entire margins were successfully delineated in 72.6% (45/62). This showed that NBI-ME was an excellent modality for identifying the entire margin of EGC when chromoendoscopy was unsuccessful. The frequency of undifferentiated EGC was significantly higher in cancers with unsuccessful delineation by NBI-ME than in cancers with successful delineation by NBI-ME.<sup>39</sup> A randomized study of NBI-ME versus indigo carmine chromoendoscopy showed that the accuracy for determination of tumor margins was significantly higher in the NBI-ME group (97.4% vs. 77.8%,  $P = 0.009$ ).<sup>40</sup>

These data suggest that C-WLI should still be incorporated in “first-line” inspection during endoscopy prior to switching to ME for a closer inspection of lesions, and then switching to NBI-ME for a better visualization of microvasculature and microsurface pattern, and also for ascertainment of tumor margins, should indigo carmine chromoendoscopy be inadequate. However, there are limitations for NBI-ME in evaluating tumor depth. Nagahama et al<sup>39</sup> found that NBI-ME failed to accurately delineate the margins of the lateral extent in 27.4% (17/63) of cancers, and subanalysis revealed that undifferentiated cancers were significantly higher among the cases of failed delineation. This was because undifferentiated cancers tend to infiltrate into the lamina propria without disturbing the surface microvascular and microsurface patterns. In 2010, an Asian Pacific consensus conference on NBI diagnosis of upper gastrointestinal cancer stated that NBI-ME was not useful for evaluation of tumor depth of EGC because of its inability to visualize submucosal invasion.<sup>16</sup>

### AFI

AFI detects the natural tissue fluorescence emitted by endogenous molecules (fluorophores) such as collagen, flavin, adenine dinucleotide, nicotinamide, and porphyrins. When these fluorophores are excited by a short-wavelength light source, they emit light of longer wavelengths. Normal tissue and neoplastic tissue have different fluorescence emissions. In AFI mode, a rotating color filter wheel in front of the xenon light source sequentially generates blue and green light to illuminate the tissues. Another interference filter in front of the AFI CCD selectively allows the tissue autofluorescence colors (of 500–630 nm wavelengths) and green light to filter through. The video processor then integrates these colors into a pseudocolor image on the screen.<sup>41</sup>

However, the role of AFI in detecting gastric neoplasia is limited by the inconsistent autofluorescence patterns in the stomach and the poor specificity. Elevated EGC lesions tend to appear purple (Fig. 5) as the collagen in the submucosal layer (which emits a green autofluorescence) may be obscured by the tumor. Depressed EGC may appear green instead. For the background color of normal mucosa, the gastric body and pylorus are normally green, whereas the gastric fundic mucosa is normally purple. In addition, mucosal

thickening or edema caused by ulceration or scarring will also look purple. Consequently, AFI can lead to a large number of false positive findings.<sup>42</sup> The sensitivity levels of AFI and C-WLI were comparable, and the specificity of AFI was actually lower than that of C-WLI because of higher false positives.<sup>43</sup>

### Trimodal imaging video endoscopy

In trimodal imaging video endoscopy, two separate monochromatic CCD are located at the tip of the endoscope for image capture; one CCD is dedicated to C-WLI and NBI, whereas the other CCD is for AFI. Switching between the imaging modes just requires pushing a button on the handle of the endoscope. This allows C-WLI, AFI, and NBI-ME to be sequentially performed in the same patient in one endoscopy session. In a prospective study conducted by Kato et al,<sup>44</sup> it was found that the addition of AFI and NBI-ME to C-WLI increased the detection rate of gastric neoplasia by 12.8%. The three modes complemented each other; NBI-ME improved the diagnostic accuracy by reducing the false positive findings associated with AFI and C-WLI, whereas AFI increased the detection of abnormal mucosa compared to C-WLI.

### Microscopic endoscopy

The term “microscopic” endoscopy suggests that endoscopists may be able to perform real-time “live” histology evaluation by using technology that enlarges the image by 500–1000 times. The optical method would be the combination of a CCD with a microscopy optical system such that the images are magnified to the point where nuclei and tissue architecture may be discernible. “Endocytoscopy” is a good term to describe this method, in which images are magnified up to 1100 times and the nuclei could be stained with dyes such as methylene blue to highlight atypical nuclear changes. The confocal method, otherwise known as confocal laser endoscopy (CLE) can magnify the image to 1000 times and requires the intravenous administration or direct spraying of fluorescent dye. It uses an argon ion laser light with a scanning depth of 0 (epithelium) to 250  $\mu\text{m}$  (lamina propria), and the reflected light is then refocused via a pinhole, which markedly increases the image resolution.<sup>45</sup> For CLE, two systems are currently available. One uses a miniaturized confocal scanner integrated into the tip of an otherwise conventional endoscope (endoscope integrated CLE; Pentax, Tokyo, Japan).

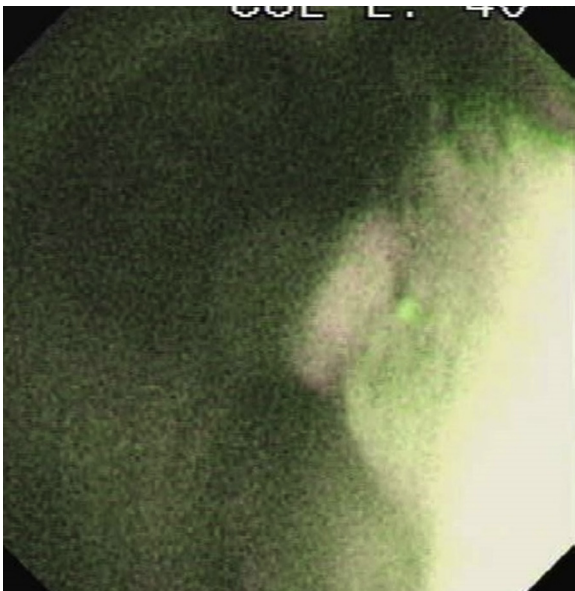


Fig. 5. Autofluorescence image of early gastric cancer.

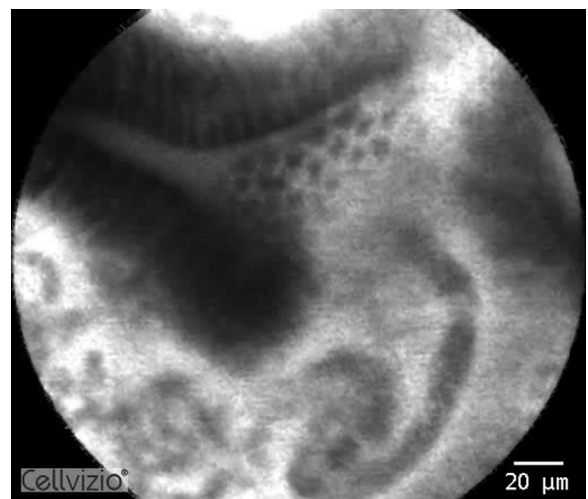


Fig. 6. Confocal image of gastric dysplasia (Courtesy of Dr. Douglas Pleskow, Beth Israel Deaconess Medical Center, Boston, MA, USA, and Mauna Kea-Technology, Paris, France.).

**Table 1 Summary of Image Enhanced Endoscopy Techniques**

	Indigo carmine chromoendoscopy	NBI	i-Scan	FICE
Overview of technique	The dye pools in the crevices of a lesion, accentuating its borders and surface topography.	A mechanical optical filter limits incident wavelengths to blue and green light, enhancing contrast between superficial vessels and mucosa.	It is a digital contrast method that applies postprocessing algorithms to white light images to enhance the image contrast.	It is a digital contrast method based on spectral estimation techniques to enhance the image contrast.
Published comparative data for early gastric cancer diagnosis	Not available	NBI-ME vs. C-WLI Maki* Sensitivity: 95% vs. 65% Specificity: 88% vs. 94% (not significant) Accuracy: 92% vs. 74% Kato† Sensitivity: 92.9% vs. 42.9% Specificity: 94.7% vs. 61% CWL + NBI-ME vs. NBI-ME vs. CWLI Ezoe‡ Sensitivity: 95% vs. 60% vs. 40% Specificity: 96.8% vs. 94.3% vs. 67.9% Accuracy: 96.6% vs. 90.4% vs. 64.8%	Comparative studies against other imaging modalities not available.	Comparative studies against other imaging modalities not available.
Qualitative assessment	Can supplement C-WLI by highlighting any subtle mucosal irregularities that could have been missed. It is routinely used to demarcate cancer margins prior to endoscopic submucosal dissection. It may be combined with optical magnification to visualize the microsurface pattern. However microvessels will not be as well visualized as by NBI. Dye-spray can be messy and laborious.	Able to provide enhanced contrast of mucosal surface. Excellent for demonstrating the morphology of fine microvessels when combined with optical magnification. The endoscopic view was dark with the older generation of NBI systems thus limiting its role in lesion detection as compared to lesion characterization but illumination is now brighter with the new generation NBI systems.	It yields bright and high contrast images of lesions.	It yields bright and high contrast images of lesions.

\* Retrospective comparative study.

† Prospective single-center comparative study.

‡ Prospective multicenter randomized study.

AFI, autofluorescence; C-WLI, conventional white light imaging; FICE, flexible spectral imaging color enhancement; NBI, narrow band imaging; NBI-ME, NBI combined with ME.

The other system in clinical use is probe-based CLE (Mauna Kea-Technology, Paris, France) and has the advantage of compatibility with most conventional endoscopes (Fig. 6). These microscopic endoscopy technologies are currently not routinely used in clinical practice, being more of research tools. In addition to the cost of obtaining the equipment, there is also a steep learning curve to using this technology, and it significantly lengthens the procedure time because of its limited field of view.

## Conclusion

HD C-WLI remains the main imaging modality for detection of focal gastric lesions. However, IEE is an important tool for the diagnosis and characterization of EGC. The relative merits, and the results of key published data of the different techniques of IEE are summarized in Table 1. In particular, there is substantial evidence that the combination of C-WLI and NBI-ME is superior to C-WLI alone or chromoendoscopy in terms of diagnostic accuracy and delineating tumor margins. In the era when endoscopic resection guidelines are being expanded, IEE should become a standard of practice as the early detection of gastric cancer allows curative treatment.

## Conflicts of interest

Both Dr M Song and Dr Tiing Leong Ang have no conflicts of interest.

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